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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,872	10/22/2003	Jane Hirsh	CP 107P	6830

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EXAMINER	
SCHLIENTZ, LEAH H	
ART UNIT	**PAPER NUMBER**
1618	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/690,872	HIRSH ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/1/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment of Receipt

Receipt of Applicant's Response, filed 12/29/06, in response to the Office Action mailed 8/31/06 is acknowledged and has been entered. The Information Disclosure Statement mailed 3/1/07 has also been entered. Claims 1 – 24 are pending.

Priority

The examiner acknowledges the priority date for the concept of a pulsatile release formulation of milnacipran to be December 5, 2002 (i.e. the filing date of the 60/431,861 application), as cited by Applicant.

Response to Arguments

The examiner acknowledges Applicant's request, on page 10 of the Response, for an interview in the event that the amendment has not placed the application in condition for allowance. Applicant is invited to telephone the examiner to schedule an interview.

Rejections under 35 U.S.C. § 112, second paragraph.

Applicant's arguments filed 12/29/06 have been fully considered but they are not persuasive. Applicant asserts on page 11 of the Response that claim 13 has been amended to specify an active metabolite of milnacipran, and accordingly that the claim, as amended, is definite. This is not found persuasive for reasons set forth hereinbelow.

Rejections under 35 U.S.C. § 102.

Applicant's arguments on page 11 of the Response, filed 12/29/06, with respect to the rejection(s) of claim(s) 1 – 9, 11 – 13, 15 – 17, 19 – 21, 23, and 24 under 35 U.S.C. § 102(b) as being anticipated by Paillard *et al.* have been fully considered and are persuasive because the extended release formulation of Paillard does not require a period of no release (lag time) as required by applicant's definition of a pulsatile release formulation on page 16 of the specification. Therefore, the rejection has been withdrawn.

Rejections under 35 U.S.C. § 103.

Applicant's arguments on pages 12 – 16 of the Response, filed 12/29/06, with respect to the rejection(s) of claim(s) 1 – 13 and 15 – 24 under 35 U.S.C. § 103(a) as being unpatentable over Paillard, in view of Watanabe, Menza, and/or Ansseau have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of newly found prior art references.

Double patenting rejections.

The provisional rejection of claims 1 – 9 and 11 – 24 under statutory-type double patenting as being unpatentable over claims 1 – 4 and 10 – 28 of copending Application 11/192,697 is maintained.

Applicant's arguments on pages 17 – 18 of the Response filed 12/29/06, with respect to the provisional rejection of claims 1 – 3, 6 – 18, and 20 – 24 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 – 3, 6 – 18, and 20 – 24 of copending Application 10/691,936 have been fully considered and are persuasive. Therefore, the provisional rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of newly found prior art references.

Applicant's arguments on pages 19 – 23 of the Response, filed 12/29/06, with respect to the rejection(s) of claim 14 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 – 3, 9, 12, and 14 – 17 of US 7,038,085 have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of newly found prior art references.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained. The claim is drawn to a milnacipran formulation, wherein the milnacipran is in the form of a therapeutically equivalent dose of an active *metabolite* of milnacipran. The claim is indefinite because

there is no guidance provided to demonstrate the chemical identity or physical characteristics of any compound which may be a milnacipran metabolite, nor is any guidance provided to describe what amount of this unspecified compound is to be included in the formulation to represent a therapeutically equivalent dosage. One would not be able to be aware of which substance is to be included in the formulation or in what amount because no indication of any specific identity or of any characteristics of such a substance is suggested in the specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 – 10, 15 – 17, and 19 – 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Midha *et al.* (US 6,340,476) in view of Ansseau *et al.* (*Psychopharmacology*, 1994, 114, p. 131 – 137).

Midha discloses that pharmaceutical dosage forms are known which provide a variety of drug release profiles, and that for some drugs it is preferred to release the drug in "pulses," wherein a single dosage form provides for an initial dose of drug, followed by a release-free interval, after which a second dose of drug is released, followed by one or more additional release-free intervals and drug release "pulses." Pulsatile drug delivery is useful, for example, with active agents that have short half-lives and must be administered two or three times daily (column 1, lines 18 – 43). The specific example of such a drug which is formulated as a pulsatile release dosage that is taught by Midha is methylphenidate, which may be used in the treatment of attention deficit disorder, narcolepsy, and depression (column 2, lines 5 – 15). Upon administration of the pulsatile release formulation, the first drug release pulse occurs within 1 – 2 hours of ingestion, which is followed by substantially no drug release, after which a second dose is released within 3 – 5 hours of ingestion, followed by a second

non-release interval. A third dose occurs from 7 – 9 hours following ingestion (column 4, lines 41+). These dosage units may be in the form of beads or particles which release the drug at different times (column 5, lines 10 – 30), of the delayed release function may be due to the presence of a coating (column 5, lines 35+). Additional active agents may be formulated to prepare a combination therapy dosage, such as amphetamines, doxapram, fluoxetine, etc. (column 8, lines 42+).

Midha fails to specifically recite that the active agent which is formulated as a pulsatile release dosage is milnacipran.

Ansseau teaches that milnacipran is a pharmaceutical which is used for the treatment of depression. Milnacipran is known to be associated with various side effects, such as nausea, insomnia, vomiting, etc. (Table 4). Studies wherein 200 mg/day of milnacipran (i.e. as 100 mg twice a day) is administered, rather than 100 mg/day once a day, are significantly more effective (page 135 – 136). When administered as a single daily dose in the evening, rather than a divided daily dose, inadequate plasma levels were obtained, likely due to the relatively short half-life of milnacipran, which is about 7 hours, with only an inactive n-dealkylated metabolite (page 136).

Ansseau does not teach a pulsatile release formulation of milnacipran.

It would have been obvious to one of ordinary skill in the art to formulate milnacipran as a pulsatile-release dosage because Midha teaches that pulsatile release formulations (i.e. of an alternative depression medication), including formulations having

a release profile within the claimed range, are useful for drugs which have a short half-life and must otherwise be administered two or three times daily (column 1, lines 18+). One would have been motivated to do so because Ansseau specifically teaches that milnacipran has only a 7 hour plasma elimination half-life, and has previously been administered in two divided daily doses (page 136). One would have had a reasonable expectation of success in using a 200 mg dosage in the formulation because Ansseau teaches that such dosages were successful in the treatment of depression.

Claims 1 – 10 and 15 – 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Midha *et al.* (US 6,340,476), in view of Ansseau *et al.* (*Psychopharmacology*, 1994, 114, p. 131 - 137), in further view of Menza *et al.* (*J. Clin. Psychiatry*, 2000, 61(5), p. 378 – 81).

Midha discloses that pharmaceutical dosage forms are known which provide a variety of drug release profiles, and that for some drugs it is preferred to release the drug in "pulses," wherein a single dosage form provides for an initial dose of drug, followed by a release-free interval, after which a second dose of drug is released, followed by one or more additional release-free intervals and drug release "pulses." Pulsatile drug delivery is useful, for example, with active agents that have short half-lives and must be administered two or three times daily (column 1, lines 18 – 43). The specific example of such a drug which is formulated as a pulsatile release dosage that is taught by Midha is methylphenidate, which may be used in the treatment of attention deficit disorder, narcolepsy, and depression (column 2, lines 5 – 15), as set forth

above. Midha also teaches the benefits of combination therapy of multiple active agents.

Midha fails to specifically recite that the active agent which is formulated as a pulsatile release dosage is milnacipran.

Ansseau teaches that milnacipran is a pharmaceutical which is used for the treatment of depression. Milnacipran is known to be associated with various side effects, such as nausea, insomnia, vomiting, etc. (Table 4). Studies wherein 200 mg/day of milnacipran (i.e. as 100 mg twice a day) is administered, rather than 100 mg/day once a day are significantly more effective (page 135 – 136). When administered as a single daily dose in the evening, rather than a divided daily dose, inadequate plasma levels were obtained, likely due to the relatively short half-life of milnacipran, which is about 7 hours, with only an inactive n-dealkylated metabolite (page 136).

Ansseau does not teach a pulsatile release formulation of milnacipran, and does not teach milnacipran in combination with modafinil.

Menza teaches a dosage of 100 to 200 mg a day of modafinil in combination with antidepressants for treatment of depression (abstract).

Menza does not teach modafinil in combination with milnacipran as the specific antidepressant.

It would have been obvious to one of ordinary skill in the art to formulate milnacipran as a pulsatile-release dosage because Midha teaches that

pulsatile release formulations (i.e. of an alternative depression medication), including formulations having a release profile within the claimed range, are useful for drugs which have a short half-life and must otherwise be administered two or three times daily (column 1, lines 18+). One would have been motivated to do so, and would have had a reasonable expectation of success in doing so, because Ansseau specifically teaches that milnacipran has only a 7 hour plasma elimination half-life, and has previously been administered in two divided daily doses (i.e. 200 mg) (page 136). It would have further been obvious to combine such a formulation with modafinil because both drugs (i.e. milnacipran and modafinil) have been used previously within the claimed dosage ranges in the treatment of depression. One would have had a reasonable expectation of success in doing so because Menza specifically teaches modafinil as an augmenter to antidepressants in the treatment of depression.

Claims 1 – 13, 15 – 17, and 19 – 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Midha *et al.* (US 6,340,476) in view of Ansseau *et al.* (*Psychopharmacology*, 1994, 114, p. 131 - 137), in further view of Paillard *et al.* (WO 98/08495).

Midha discloses that pharmaceutical dosage forms are known which provide a variety of drug release profiles, and that for some drugs it is preferred to release the drug in "pulses," wherein a single dosage form provides for an initial dose of drug, followed by a release-free interval, after which a second dose of drug is released, followed by one or more additional release-free intervals and drug release "pulses."

Pulsatile drug delivery is useful, for example, with active agents that have short half-lives and must be administered two or three times daily (column 1, lines 18 – 43). The specific example of such a drug which is formulated as a pulsatile release dosage that is taught by Midha is methylphenidate, which may be used in the treatment of attention deficit disorder, narcolepsy, and depression (column 2, lines 5 – 15), as set forth above. Midha also teaches the benefits of combination therapy of multiple active agents.

Midha fails to specifically recite that the active agent which is formulated as a pulsatile release dosage is milnacipran.

Ansseau teaches that milnacipran is a pharmaceutical which is used for the treatment of depression. Milnacipran is known to be associated with various side effects, such as nausea, insomnia, vomiting, etc. (Table 4). Studies wherein 200 mg/day of milnacipran (i.e. as 100 mg twice a day) is administered, rather than 100 mg/day once a day are significantly more effective (page 135 – 136). When administered as a single daily dose in the evening, rather than a divided daily dose, inadequate plasma levels were obtained, likely due to the relatively short half-life of milnacipran, which is about 7 hours, with only an inactive n-dealkylated metabolite (page 136).

Ansseau does not teach a pulsatile release formulation of milnacipran, and does not teach enantiomers of milnacipran.

Paillard teaches a pharmaceutical composition for prolonged release of a single daily dose of 50 to 240 mg of milnacipran (column 1, lines 30 – 35). A racemic mixture or pure enantiomeric form of milnacipran may be administered (column 1, line 65 – column 2, line 3). The formulation comprises a mixture of microparticles that release the drug at different times (column 1, line 30 – 53), and side effects of the drug are reduced. The microparticles contain a coating such as Eudragit NE30D, RS 100, RL 100, etc. (column 6, lines 45 – 68).

Paillard teaches an extended release, rather than a pulsatile release, formulation of milnacipran.

It would have been obvious to one of ordinary skill in the art to formulate milnacipran as a pulsatile-release dosage because Midha teaches that pulsatile release formulations (i.e. of an alternative depression medication), including formulations having a release profile within the claimed range, are useful as an alternative to immediate-release or extended-release formulations for drugs which have a short half-life and must otherwise be administered two or three times daily (column 1, lines 18+). One would have been motivated to do so, and would have had a reasonable expectation of success in doing so, because Ansseau specifically teaches that milnacipran has only a 7 hour plasma elimination half-life, and has previously been administered in two divided daily doses (i.e. 200 mg) (page 136). It would have further been obvious to include an enantiomer of milnacipran in the formulation because Paillard teaches that cis and trans enantiomers may be used in modafinil formulations for the treatment of depression.

Claims 1 – 3, 6 – 17, 20, and 23 are rejected under 35 USC 103(a) as being unpatentable over Rao *et al.* (US 2003/0203055).

Rao discloses various pharmaceutical compositions comprising milnacipran (paragraph 0011), including the enantiomers or the para-hydroxylated derivative of milnacipran (paragraph 0106 – 0107). The milnacipran dosage is typically about 100 mg/70 kg body weight (paragraph 0110). Selective norepinephrine (NE)-serotonin (5-HT) reuptake inhibitors (e.g., milnacipran) can be administered adjunctively with other active compounds such as a medicament for the treatment of dysphagia, dyspepsia, aerophagia, irritable bowel syndrome, abdominal bloating, constipation, etc. (paragraph 0133). Milnacipran may be coadministered with a corticosteroid, a glucocorticoid, acetazolamide, carbamazepine, clonazepam, ethosuximide, fosphenytoin, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone, topiramate, valproate, a barbiturate, benzodiazepine, modafinil, etc. (paragraph 0137). The compositions may be formulated to include a combination of an immediate release portion and a sustained release formulation (example 41).

It is noted that Rao does not specifically recite that the compositions are "pulsatile release" formulations of milnacipran. However, in the absence of evidence to the contrary, it is interpreted that it would have been obvious to one of ordinary skill in the art that such a formulation would result in at least one "pulse" of the active ingredient, and as such a formulation is within the scope of a formulation which releases at least one pulse of active ingredient and which results in a decrease in dosing frequency. The instant claims are defined only by function and are devoid of any

structural limitations, other than that the composition comprises a coating, which is also present in the formulations taught by Rao.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

The provisional rejection of claims 1 – 9 and 11 – 24 under 35 U.S.C. 101 as claiming the same invention as that of claims 1 – 4 and 10 – 28 of copending Application 11/192,697 is maintained. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 – 3, 6 – 18, and 20 – 24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 3, 6 – 18, and 20 – 24 of copending Application No. 10/691,936 in view of Midha *et al.* (US 6,340,476) in view of Ansseau *et al.* (*Psychopharmacology*, 1994, 114, p. 131 - 137). This is a provisional obviousness-type double patenting rejection.

The cited claims of the '936 application are drawn to an extended release formulation of milnacipran and methods of treating depression therewith. The '936 application does not claim a pulsatile release formulation.

Midha discloses that pharmaceutical dosage forms are known which provide a variety of drug release profiles, and that for some drugs it is preferred to release the drug in "pulses," wherein a single dosage form provides for an initial dose of drug, followed by a release-free interval, after which a second dose of drug is released, followed by one or more additional release-free intervals and drug release "pulses." Pulsatile drug delivery is useful, for example, with active agents that have short half-lives and must be administered two or three times daily (column 1, lines 18 – 43). The specific example of such a drug which is formulated as a pulsatile release dosage that is taught by Midha is methylphenidate, which may be used in the treatment of attention

deficit disorder, narcolepsy, and depression (column 2, lines 5 – 15). Midha fails to specifically recite that the active agent which is formulated as a pulsatile release dosage is milnacipran.

Ansseau teaches that milnacipran is a pharmaceutical which is used for the treatment of depression. Milnacipran is known to be associated with various side effects, such as nausea, insomnia, vomiting, etc. (Table 4). Studies wherein 200 mg/day of milnacipran (i.e. as 100 mg twice a day) is administered, rather than 100 mg/day once a day are significantly more effective (page 135 – 136). When administered as a single daily dose in the evening, rather than a divided daily dose, inadequate plasma levels were obtained, likely due to the relatively short half-life of milnacipran, which is about 7 hours, with only an inactive n-dealkylated metabolite (page 136). Ansseau does not teach a pulsatile release formulation of milnacipran.

It would have been obvious to one of ordinary skill in the art to formulate milnacipran as a pulsatile-release dosage as an alternative to immediate release, extended release, etc. formulations because the '936 application claims an extended release pharmaceutical formulations of milnacipran which is used for the treatment of depression, and Midha teaches that pulsatile release formulations of another depression medication are known in the art to be useful for drugs which have a short half-life and must otherwise be administered two or three times daily (column 1, lines 18+), and are well-known in the art to be an alternative to extended release, etc. formulations, and because Ansseau teaches that milnacipran has a relatively short half-life and has been administered in twice-daily doses.

Claim 14 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 3 and 9 of U.S. Patent No. 7,038,085 in view of Midha *et al.* (US 6,340,476) in view of Ansseau *et al.* (*Psychopharmacology*, 1994, 114, p. 131 - 137).

The '085 patent claims enantiomers of para-hydroxy milnacipran and pharmaceutical formulations thereof for the treatment of depression (claims 1 – 3, 9, and 12). The '085 patent does not specifically claim that the pharmaceutical formulation of para-hydroxy milnacipran is a pulsatile-release formulation.

Midha discloses that pharmaceutical dosage forms are known which provide a variety of drug release profiles, and that for some drugs it is preferred to release the drug in "pulses," wherein a single dosage form provides for an initial dose of drug, followed by a release-free interval, after which a second dose of drug is released, followed by one or more additional release-free intervals and drug release "pulses." Pulsatile drug delivery is useful, for example, with active agents that have short half-lives and must be administered two or three times daily (column 1, lines 18 – 43). The specific example of such a drug which is formulated as a pulsatile release dosage that is taught by Midha is methylphenidate, which may be used in the treatment of attention deficit disorder, narcolepsy, and depression (column 2, lines 5 – 15). Midha fails to specifically recite that the active agent which is formulated as a pulsatile release dosage is a milnacipran derivative.

Ansseau teaches that milnacipran is a pharmaceutical which is used for the treatment of depression. Milnacipran is known to be associated with various side effects, such as nausea, insomnia, vomiting, etc. (Table 4). Studies wherein 200 mg/day of milnacipran (i.e. as 100 mg twice a day) is administered, rather than 100 mg/day once a day are significantly more effective (page 135 – 136). When administered as a single daily dose in the evening, rather than a divided daily dose, inadequate plasma levels were obtained, likely due to the relatively short half-life of milnacipran, which is about 7 hours, with only an inactive n-dealkylated metabolite (page 136). Ansseau does not teach a pulsatile release formulation of a milnacipran derivative.

It would have been obvious to one of ordinary skill in the art to formulate a milnacipran derivative, para-hydroxy milnacipran, as a pulsatile-release dosage as an alternative to immediate release, extended release, etc. formulations because the '085 claims that pharmaceutical formulations of para-hydroxy milnacipran are used for the treatment of depression, and Midha teaches that pulsatile release formulations of another depression medication are well-known in the art to be useful for drugs which have a short half-life and must otherwise be administered two or three times daily (column 1, lines 18+) as an alternative to immediate release, extended release, etc. formulations, and because Ansseau teaches that milnacipran has a relatively short half-life and has been administered in twice-daily doses.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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